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Original article

Effects of HMG-CoA reductase inhibitors on continuous post-inflammatory vascular remodeling late after Kawasaki disease

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KEYWORDS

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Arteriosclerosis;
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Summary

Background: In Kawasaki disease (KD), it has been clinically and experimentally reported that post-inflammatory vascular remodeling would induce the development of arteriosclerosis or early onset of atherosclerosis in the future. The effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors on continuous vascular remodeling late after Kawasaki disease were clinically evaluated.

Patients and methods: We enrolled and treated a total of 11 KD patients (age range, 7–25 years) with fluvastatin (0.5–0.7 mg/kg/day) for 12 months. All of them had significant coronary aneurysmal or stenotic lesions and more than 3 of the following 5 abnormal findings: reduced %flow-mediated dilatation (%FMD), reduced urinary NOx, elevated high-sensitivity C-reactive protein (hs-CRP), reduced urinary 8-isoprostane, and elevated brachial-ankle pulse wave velocity (baPWV; control, ≤ 1400 cm/s).

Results: A statistically significant improvement was observed in each biomarker after fluvastatin treatment: %FMD, from 9.29% (3.41)% to 10.55% (3.27)% ($p=0.003$) after 3 months; NOx/creatinine (cre), from 1.16 (0.54) $\mu\text{mol}/\text{mg}$ cre to 1.30 (0.50) $\mu\text{mol}/\text{mg}$ cre ($p=0.038$) after 12 months; baPWV, from 1175.4 (277.3) cm/s to 1031.8 (155.6) cm/s ($p=0.009$) after 3 months; hs-CRP, from 0.073 (0.035) mg/dl to 0.028 (0.014) mg/dl ($p=0.0002$) after 3 months; and 8-iso/cre, from 751.8 (241.8) pg/mg cre to 660.0 (198.5) pg/mg cre ($p=0.018$) after 3 months. No adverse events were clinically observed in the patients.

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Conclusions: The results of this study suggested that HMG-CoA reductase inhibitors are useful as an alternative therapeutic strategy for stabilizing continuous post-inflammatory vascular remodeling that results in the development of arteriosclerosis late after KD or early onset of atherosclerosis in the future.

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Introduction

Kawasaki disease (KD) is an acute febrile disorder of unknown etiology that mainly affects infants and young children [1–3]. It is characterized by systemic vasculitis. The most common and serious clinical feature is the involvement of the coronary arteries, which results in aneurysmal changes that can lead to the development of stenotic lesions or myocardial ischemia associated with late mortality [4,5]. Even in transient dilatated and regressed coronary lesions, intimal thickening associated with arteriosclerotic changes has been detected by imaging using two-dimensional echocardiography, magnetic resonance imaging (MRI), and intravascular ultrasonography with virtual histology [6,7]. In addition, even in adolescents and adults who did not have coronary lesions, endothelial dysfunction [determined by measuring the coronary flow reserve, flow-mediated dilatation (FMD) of the brachial artery, and urinary NOx], persistent inflammation [determined by measuring high-sensitivity C-reactive protein (hs-CRP) levels], and oxidative stress were noted [8–11]. Moreover, there is clinical and experimental evidence [12,13] in support of a history of KD as a risk factor for the early onset or progression of atherosclerosis [14,15]. Therefore, it is necessary to develop a new therapeutic strategy for preventing the early onset or progression of atherosclerosis in patients with a history of KD.

Recently, it has been demonstrated that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which act through both cholesterol-dependent and cholesterol-independent mechanisms, significantly reduce the likelihood of major coronary events [16–18]. Recent studies have also revealed that HMG-CoA reductase inhibitors have an anti-inflammatory effect, and improve endothelial dysfunction and oxidative stress, which are significant markers of the early progression of atherosclerosis [19–22]. Therefore, these inhibitors could prevent the progression of arteriosclerosis or atherosclerosis in KD patients, but this is yet to be studied.

In this study, we aimed to evaluate the therapeutic effects of HMG-CoA reductase inhibitors on the prevention of continuous post-inflammatory vascular remodeling resulting in the development of arteriosclerosis in KD patients. To do so, we treated KD patients with HMG-CoA reductase inhibitors late after the onset of KD and examined the changes in various biochemical and physiological biomarkers associated with endothelial function, arterial stiffness, vascular wall inflammation, and oxidative stress.

Patients and methods

In this study, we enrolled 11 Japanese patients with KD [mean (SD) age, 14.5 (6.1) years; range, 7–25 years] (Table 1). All patients had coronary artery lesions and more

than 3 of the following 5 abnormal findings: reduced %FMD, low urinary NOx levels, increased brachial-ankle pulse wave velocity (baPWV), increased hs-CRP levels, and high urinary 8-isoprostane levels, compared with the age-matched control values previously reported (%FMD, $14.4 \pm 3.2\%$; urinary NOx, $1.22 \pm 0.92 \mu\text{mol/mg creatinine (cre)}$; baPWV, $\leq 1400 \text{ cm/s}$; hs-CRP, $0.035 \pm 0.05 \text{ mg/dl}$) [11]. The interval between the onset of KD and the start of this study was 4–22 years [mean (SD), 12.4 (6.0) years]. All the patients met the clinical criteria for KD and had acute or healed coronary artery lesions, as documented by coronary angiography. These patients were followed up at our university hospital. They received anticoagulant therapy, but none of them received angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic blockers, calcium channel antagonists, or nitrates. All the subjects were non-smokers and had no history of hypertension, hyperglycemia, or hypercholesterolemia. All the subjects continued to take anti-thrombotic drugs, but they were advised not to consume too much vitamins C and E and polyphenols; they were also instructed not to perform strenuous exercises on the day before the examination. This study was approved by the ethics committee of our university. Written informed consent to the study protocol was obtained from all the patients and their parents.

The study protocol was as follows. We measured the %FMD and urinary NOx as markers of endothelial function [23–26], baPWV as a marker of arterial stiffness [27–29], hs-CRP as a marker of vascular wall inflammation [30,31], and urinary 8-isoprostane as a marker of oxidative stress [25,26]. These parameters were measured before treatment and 3, 6, and 12 months after initiating the administration of the HMG-CoA reductase inhibitor fluvastatin ($0.5\text{--}0.7 \text{ mg/kg/day}$). The dose of fluvastatin was controlled so that the total serum cholesterol level was maintained above 120 mg/kg in each subject, since this is the required level of cholesterol in the body. All examinations were performed in the morning.

Samples of urine and venous blood were collected in bottles, immediately aliquoted, and stored at -80°C . %FMD was measured using high-resolution ultrasonography with a 12.0-MHz linear-array transducer (Vivid 3; GE Medical Systems, Fairfield, CT, USA) as previously described [11]. Capillary electrophoresis was performed using a Quanta 4000 system (Waters Corp., Milford, MA, USA) to determine the concentration of urinary NOx [32]. The levels of urinary NOx were standardized with those of urinary cre (NOx/cre; units, $\mu\text{mol/mg cre}$). baPWV was measured using a noninvasive volume plethysmographic technique (form PWV/ABI; Colin Co., Komaki, Japan) [27,33], and hs-CRP was measured using the latex agglutination reaction. Urinary 8-isoprostane [34–36] was measured using ELISA, and its levels were stan-

Table 1 Clinical profile of the patients.

Case	Gender	Age at onset (year)	Age at this study (year)	CAL in acute phase	CAL at this study	Medication	Ischemic events
1	F	3	10	ANm (RCA)	AN, LS (RCA)	A, W, D	—
2	M	1	13	ANm (B-CA)	AN, LS (RCA, LCA)	A, W	—
3	M	2	22	ANl (B-CA)	REC (RCA), AN (LCA)	A, D	—
4	M	1	7	ANm (RCA)	ANm (RCA)	A, W	—
5	M	2	21	ANl (B-CA)	REC (RCA), AN (LCA)	A, W, D	—
6	F	4	9	ANm (B-CA)	AN (LCA), LS (RCA)	A, W	—
7	F	3	13	ANm (RCA)	AN, LS (RCA)	A	—
8	M	3	25	ANl (B-CA)	REC (RCA), AN (LCA)	A, W	—
9	M	1	8	ANm (LCA)	AN, LS (LCA)	A, P	—
10	M	2	18	ANl (B-CA)	REC (RCA), AN (LCA)	A, W	—
11	M	1	14	ANm (LCA)	ANm (LCA)	A, W	—

CAL, coronary artery lesion; AN, aneurysm; ANm, medium-sized aneurysm; ANl, large-sized aneurysm; RCA, right coronary artery; LCA, left coronary artery; B-CA, coronary arteries of both sides; LS, localized stenosis; REC, recanalization; A, aspirin; W, warfarin; D, dipyridamole.

dardized with those of urinary cre (8-iso/cre; units, pg/mg cre).

Statistical analysis

All values are expressed as mean (SD) unless otherwise specified. All data analyses were performed using the SPSS 13.0J software (SPSS, Chicago, IL, USA). The values obtained before and after fluvastatin treatment were statistically analyzed using the paired *t*-test. A *p*-value of less than 0.05 was considered statistically significant.

Results

The clinical profile of the subjects is shown in Table 1. All the subjects had some form of coronary artery lesion, including stenotic lesions, but none had a history of myocardial ischemia. The electrocardiogram findings and left ventricular wall motion, studied using two-dimensional echocardiography, were normal in all the subjects. Before the fluvastatin treatment, the subjects had significantly low %FMD [$p < 0.05$; 9.29% (3.41%) vs. 14.4% (3.2%)], and had significantly high hs-CRP [$p < 0.05$; 0.073 (0.035) mg/dl vs. 0.016 (0.006) mg/dl] and 8-iso/cre [$p < 0.05$; 751.8 (241.8) pg/mg cre vs. 512.2 (272.2) pg/mg cre] compared to the controls. There were no statistically significant differences between the subjects and controls in NOx/cre [1.16 (0.54) μ mol/mg cre vs. 1.22 (0.92) μ mol/mg cre] and baPWV [1175.4 (277.3) cm/s vs. 1161 (114) cm/s].

%FMD and urinary NOx as markers of endothelial function

The values of %FMD changed during the 12-month fluvastatin treatment period (Table 2 and Fig. 1). %FMD

significantly increased from 9.29% (3.41%) before the initiation of treatment to 10.55% (3.27%) ($p = 0.003$) after 3 months, 10.68% (3.24%) ($p = 0.0003$) after 6 months, and 10.87% (3.11%) ($p = 0.0004$) after 12 months (Fig. 1). For urinary NOx/cre ratio, there were no statistically significant differences between the value before the treatment [1.16 (0.54) μ mol/mg cre], 3 months [1.20 (0.54) μ mol/mg cre] and 6 months [1.24 (0.45) μ mol/mg cre] after the treatment. However, the NOx/cre significantly increased to 1.30 (0.50) μ mol/mg cre after 12 months (Fig. 2).

baPWV as a marker of arterial stiffness

baPWV changed during the 12-month fluvastatin treatment period (Table 2 and Fig. 3); it significantly decreased from 1175.4 (277.3) cm/s before treatment initiation to 1031.8 (155.6) cm/s ($p = 0.009$) after 3 months, 1014 (161.9) cm/s ($p = 0.001$) after 6 months, and 1027.2 (166.4) cm/s ($p = 0.001$) after 12 months.

hs-CRP as a marker of inflammation

The values of serum hs-CRP changed during the 12-month fluvastatin treatment period (Table 2 and Fig. 4). The hs-CRP value before fluvastatin treatment was 0.073 (0.035) mg/dl, which is significantly higher ($p < 0.05$) than our repeated value of 0.016 (0.006) mg/dl in age-matched KD patients ($n = 20$) without any cardiac lesions. The hs-CRP values significantly decreased to 0.028 (0.014) mg/dl ($p = 0.0002$) after 3 months, 0.024 (0.007) mg/dl ($p = 0.0002$) after 6 months, and 0.020 (0.007) mg/dl ($p = 0.0001$) after 12 months of fluvastatin treatment. These reductions in serum hs-CRP remained steady during the 12-month fluvastatin treatment.

Table 2 Changes in the parameters of the subjects before and after fluvastatin treatment.

Parameters	Before	After initiating fluvastatin treatment			p-Value at 12 months
		3 months	6 months	12 months	
% FMD	9.29 ± 3.41	10.55 ± 3.27*	10.68 ± 3.24*	10.87 ± 3.11*	0.0004
NOx/cre	1.16 ± 0.54	1.20 ± 0.54	1.24 ± 0.45	1.30 ± 0.50*	0.038
baPWV	1175.4 ± 277.3	1031.8 ± 155.6*	1014.5 ± 161.9*	1027.2 ± 166.4*	0.001
hs-CRP	0.073 ± 0.003	0.028 ± 0.014*0.0	-0.024 ± 0.007*	0.020 ± 0.007*	0.0001
8-iso/cre	751.8 ± 241.8	660.0 ± 198.5*	626.3 ± 181.8*	609.1 ± 183.8*	0.001
Total cholesterol	171.1 ± 13.1	144.2 ± 8.6*	143.6 ± 9.8*	144.1 ± 7.8*	0.00001

Results are expressed as mean (SD). %FMD, percent flow-mediated dilatation; NOx/cre, NOx/creatinine; baPWV, pulse wave velocity of the brachial artery; hs-CRP, high-sensitivity C-reactive protein; 8-iso/cre, 8-isoprostane/creatinine.

* $p < 0.05$ vs. the pre-treatment values.

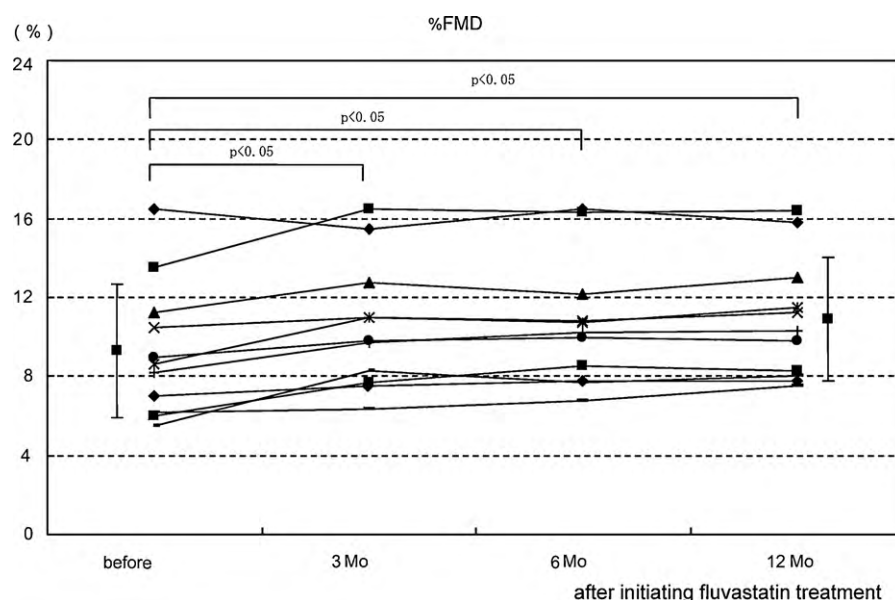


Figure 1 Changes in percent flow-mediated dilatation (%FMD) in subjects treated with fluvastatin for 12 months. Bar shows mean (SD). * $p < 0.05$ vs. the pre-treatment values.

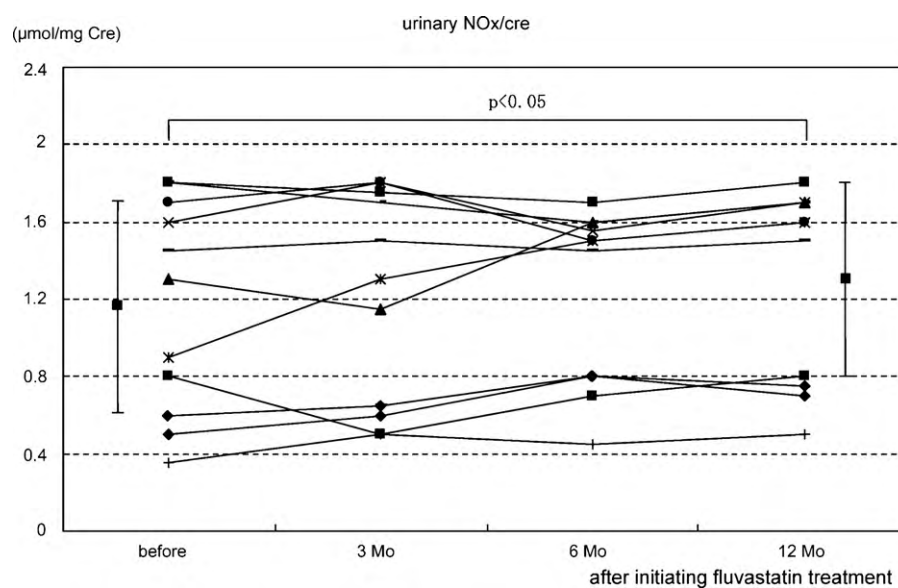


Figure 2 Changes in urinary NOx/creatinine (cre) values in subjects treated with fluvastatin for 12 months. Bar shows mean (SD). * $p < 0.05$ vs. the pre-treatment values.

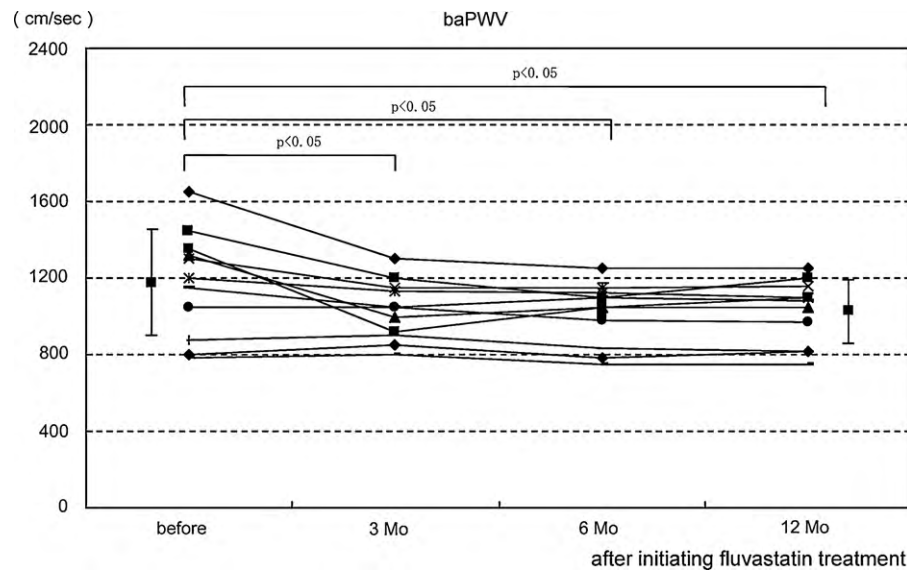


Figure 3 Changes in the pulse wave velocity of the brachial artery (baPWV) in subjects treated with fluvastatin for 12 months. Bar shows mean (SD). * $p < 0.05$ vs. the pre-treatment values.

8-Iso/cre as a marker of oxidative stress

The 8-iso/cre ratio changed during the 12-month fluvastatin treatment period (Table 2 and Fig. 5). The 8-iso/cre value before fluvastatin treatment was 751.8 (241.8) pg/mg cre; this value is significantly higher ($p < 0.05$) than our reported value of 512.2 (272.2) pg/mg cre in age-matched KD patients ($n=20$) without any cardiac lesions. After fluvastatin treatment was initiated, the 8-iso/cre ratio significantly decreased to 660.0 (198.5) ($p=0.018$) after 3 months, 626.3 (181.8) ($p=0.009$) after 6 months, and 609.1 (183.8) ($p=0.0014$) after 12 months.

Serum cholesterol as a marker of fluvastatin dose

The values of total serum cholesterol changed during the 12-month fluvastatin treatment period (Table 2 and Fig. 6). The total serum cholesterol level significantly decreased from 171.1 (13.1) mg/dl to 144.2 (8.63) mg/dl ($p=0.000014$) after 3 months, 143.6 (9.84) mg/dl ($p=0.000043$) after 6 months, and 144.1 (7.85) mg/dl ($p=0.000012$) after 12 months of fluvastatin treatment. We controlled the dose of fluvastatin not to decrease total serum cholesterol value under 120 mg/dl. Additionally, during the fluvastatin treatment, none of the patients had any significant symptom including leg pain, or abnormal laboratory data in the hepatic function and CK.

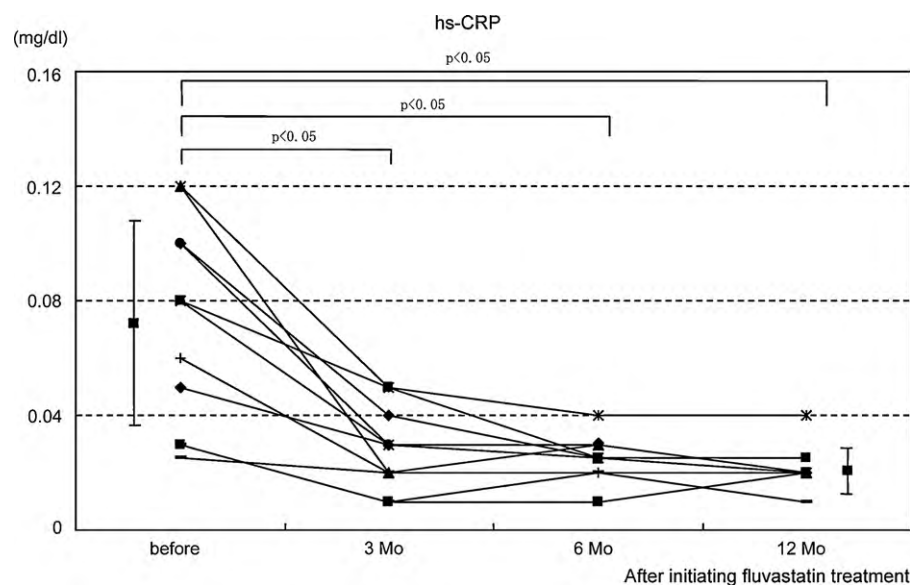


Figure 4 Changes in the serum high-sensitivity C-reactive protein (hs-CRP) values in subjects treated with fluvastatin for 12 months. Bar shows mean (SD). * $p < 0.05$ vs. the pre-treatment values.

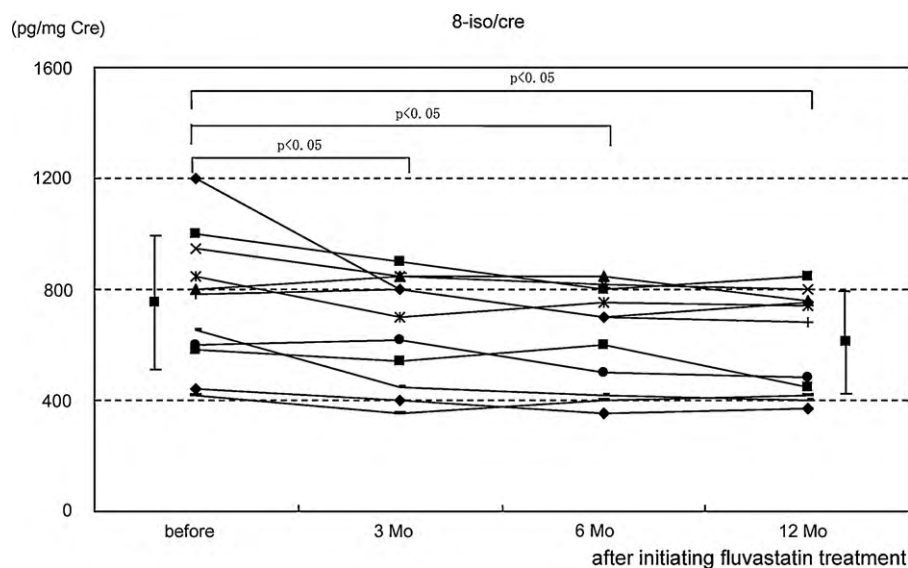


Figure 5 Changes in the urinary 8-isoprostane/creatinine (8-iso/cre) ratio in subjects treated with fluvastatin for 12 months. Bar shows mean (SD). * $p < 0.05$ vs. the pre-treatment values.

Discussion

In the present study, we have evaluated the effects of fluvastatin administration on %FMD, urinary NOx (both markers of vascular endothelial function), baPWV (marker of arterial stiffness), hs-CRP (marker of chronic inflammation), and urinary 8-isoprostane (marker of oxidative stress). A significant improvement was observed in each of these markers after the administration of fluvastatin. We selected these markers because (1) recently, a markedly advanced molecular biological method was used to analyze the pathogenic mechanism of arteriosclerosis or atherosclerosis, and the above markers were found to be associated with vascular remodeling and the subsequent development of arteriosclerosis or atherosclerosis, and (2) these markers have been

widely used to assess the clinical conditions or treatment of atherosclerosis in adult patients with obesity, hypertension, hyperlipidemia, or diabetes mellitus [26–32,37].

It has been suggested that KD eventually leads the development of post-inflammatory arteriosclerosis [2,3]. Further, it was reported that arteriosclerosis develops early at the site of the morphological changes by clinically apparent coronary aneurysms [4,5,38]. However, these are studied only in patients with giant aneurysms. The functional and biological states of chronic vascular lesions can be investigated with a recently developed method.

We evaluated blood flow and current fluctuations of the coronary artery with thermodilution and a Doppler guidewire, respectively. Even in patients with no apparent coronary arterial lesions, very small vascular lesions or

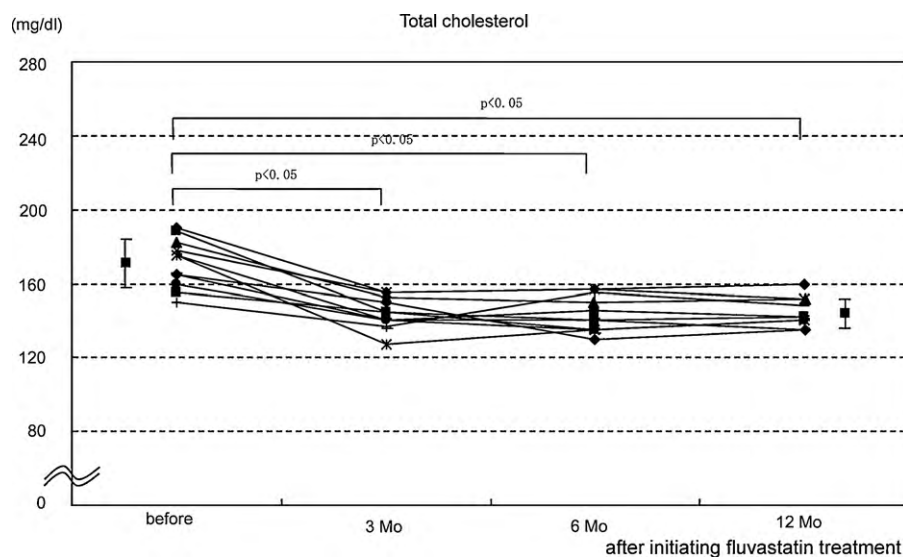


Figure 6 Changes in the total blood cholesterol in subjects treated with fluvastatin for 12 months. Bar shows mean (SD). * $p < 0.05$ vs. the pre-treatment values.

disorders in coronary artery vasodilatation were persisting. Moreover, a functional abnormality was found in the systemic vascular endothelium [8–10]. We have also reported the risk of early onset of arteriosclerosis in patients with changes in the vascular endothelium, oxidative stress, and persisting inflammation in the chronic phase of KD [11].

Thereafter, several studies have indicated the persistence of functional disorders and inflammation in the chronic phase of KD.

Intimal hypertrophy associated with arteriosclerosis has been detected in coronary vessels with the help of diagnostic imaging such as intravascular ultrasonography and MRI; the hypertrophy normalized after temporary enlargement of the vessels [6,7,39,40].

These findings indicate that vasculitis associated with KD can potentially develop into arteriosclerosis over a long period of time. It therefore follows that controlling the development of blood vessel disorders into arteriosclerosis is important for improving long-term prognosis of KD. However, no treatment strategy to this effect has been established yet.

In recent years, strategies to prevent the development of arteriosclerosis in adults with conditions such as hypertension, diabetes mellitus, obesity, and hyperlipidemia have been studied extensively. In these studies, HMG-CoA reductase inhibitors were shown to have favorable clinical effects. They decrease the serum cholesterol level by inhibiting HMG-CoA reductase at the rate-controlling step of cholesterol synthesis; they have therefore been used as therapeutic agents for hyperlipidemia in clinical practice. Since then, HMG-CoA reductase inhibitors have been proven to have different pharmacological activities such as anti-inflammatory and anti-oxidative activities, and to improve vascular endothelial function [16,17,19–22,41]. Therefore, HMG-CoA reductase inhibitors have attracted much attention as drugs for arteriosclerosis.

It has been reported that even in adolescent and young children, coronary risk factors such as diabetes or hypercholesterolemia lead to vascular endothelial dysfunction and oxidative stress resulting in arteriosclerotic changes. It has also been reported that the endothelial function was improved by controlling these factors.

However, for children, there are few reports that HMG-CoA reductase inhibitors are effective directly against these risk factors. HMG-CoA reductase inhibitors' pleiotropic effects for adults have been licensed, so now we can expect their clinical application for children [42–45].

Since the pathological mechanism of the development of inflammatory atherosclerotic lesions in infants and young individuals has not been completely elucidated, there is no effective method for assessing the function of blood vessels in KD patients. Therefore, the efficacy of HMG-CoA reductase inhibitors has not been studied by clinical investigation.

We developed an animal model of KD, which is similar to the model of vasculitis in juvenile rabbits, and clearly demonstrated the anti-inflammatory activities of HMG-CoA reductase inhibitors against the progress of acute vasculitis [46,47]. The present clinical investigation was conducted on the basis of the results obtained in these animal experiments.

We found a significant improvement in the levels of all five markers after fluvastatin administration. This effect was

found as early as 3 months later and continued during the 12 months of administration. We found that the continuous post-inflammatory vascular remodeling, which results in the development of arteriosclerosis, was significantly stabilized by the administration of HMG-CoA reductase inhibitors late after KD. From these observations, it is anticipated that they may also be effective for the early stabilization of coronary lesions during the acute to convalescent periods of KD. Moreover, they probably suppress the long-term development of potential atherosclerosis. We believe that to improve the long-term prognosis of blood vessel disorders in KD patients, a therapeutic approach using HMG-CoA reductase inhibitors might be an alternative to the present strategies such as anticoagulant therapy.

Because the sample size was small, the present study was a preliminary investigation with limited indications. Although it was possible to suppress the development of post-inflammatory arteriosclerosis by administering HMG-CoA reductase inhibitors, further studies are necessary to determine the indications or administration periods of the drug in KD patients receiving concurrent medication.

The primary pharmacological activity of HMG-CoA reductase inhibitors is to decrease the blood cholesterol level. Cholesterol plays an important role in biological functions and is absolutely necessary in the body. Keeping this in mind, particularly in the case of children and pubertal individuals, we adjusted the dose of HMG-CoA reductase inhibitors so that the level of blood cholesterol remained above 120 mg/dl in all the patients [48–51]. No significant adverse reactions or complications occurred during the study; however, we have not investigated several parameters such as optimum dosage, time of administration, and type of HMG-CoA reductase inhibitor. Large-scale clinical investigations will be required to determine these factors.

Conclusion

In this study, we found that HMG-CoA reductase inhibitors stabilized endothelial dysfunction, arterial stiffness, oxidative stress, and chronic vascular inflammation in KD patients with coronary artery lesions. Therefore, we think that HMG-CoA reductase inhibitors have the potential to prevent the development of post-inflammatory arteriosclerosis late after KD and early onset of atherosclerosis in the future.

References

- [1] Kawasaki T. Acute febrile muco-cutaneous lymph node syndrome in young children with unique digital desquamation. *Jpn J Allergol* 1967;16:178–222.
- [2] Fujiwara H, Hamashima Y. Pathology of the heart in Kawasaki disease. *Pediatrics* 1978;61:100–7.
- [3] Naoe S, Shibuya K, Takahashi K, Wakayama M, Masuda H, Tanaka N. Pathological observation concerning the cardiovascular lesions in Kawasaki disease. *Cardiol Young* 1991;1:206–12.
- [4] Akagi T, Rose V, Benson LN, Newman A, Freedome RM. Outcome of coronary artery aneurysm after Kawasaki disease. *J Pediatr* 1992;121:689–94.
- [5] Onouchi Z, Hamaoka K, Sakata K, Ozawa S, Shiraishi I, Itoi T, Kiyosawa N. Long-term changes in coronary artery aneurysms in patients with Kawasaki disease: comparison of therapeutic regimens. *Circ J* 2005;69:265–72.

- [6] Iemura M, Ishii M, Sugimura T, Akagi T, Kato H. Long term consequences of regressed coronary aneurysms after Kawasaki disease: vascular wall morphology and function. *Heart* 2000;83:307–11.
- [7] Mitani Y, Ohashi H, Sawada H, Ikeyama Y, Hayakawa H, Takabayashi S, Maruyama K, Shimpo H, Komada Y. In vivo plaque composition and morphology in coronary artery lesions in adolescents and young adults long after Kawasaki disease: a virtual histology-intra vascular ultrasound study. *Circulation* 2009;119:2829–36.
- [8] Hamaoka K, Onouchi Z, Kamiya Y, Sakata K. Evaluation of coronary flow reserve velocity dynamics and flow reserve in patients with Kawasaki disease by means of a Doppler guide wire. *J Am Coll Cardiol* 1998;31:833–40.
- [9] Hamaoka K, Onouchi Z, Ohmochi Y. Coronary flow reserve in children with Kawasaki disease without angiographic evidence of coronary stenosis. *Am J Cardiol* 1992;69:691–2.
- [10] Hamaoka K, Onouchi Z. Effects of coronary artery aneurysms on intracoronary flow velocity dynamics in Kawasaki disease. *Am J Cardiol* 1996;77:873–5.
- [11] Niboshi A, Hamaoka K, Sakata K, Yamaguchi N. Endothelial dysfunction in adult patients with a history of Kawasaki disease. *Eur J Pediatr* 2008;167:189–96.
- [12] Onouchi Z, Ikuta K, Nagamatsu K, Tamiya H, Sakakibara Y, Ando M. Coronary artery aneurysms develop in weaning rabbits with serum sickness but not in mature rabbits. An experimental model for Kawasaki disease in humans. *Angiology* 1995;46:679–87.
- [13] Liu Y, Onouchi Z, Sakata K, Ikuta K. An experimental study on the role of smooth muscle cells in the pathogenesis of atherosclerosis of the coronary arteritis. *J Jpn Pediatr Soc* 1996;100:1453–8.
- [14] Noto N, Okada T, Yamasuge M, Taniguchi K, Karasawa K, Ayusawa M, Sumitomo N, Harada K. Noninvasive assessment of the early progression of atherosclerosis in adolescents with Kawasaki disease and coronary artery lesions. *Pediatrics* 2001;107:1095–9.
- [15] Takahashi K, Oharaseki T, Naoe S. Pathological study of postcoronary arteritis in adolescents and young adults: with reference to the relationship between sequelae of Kawasaki disease and atherosclerosis. *Pediatr Cardiol* 2001;22:138–42.
- [16] Lewis SJ, Sacks FM, Mitchell JS, East C, Glasser S, Kell S, Letterer R, Limacher M, Moye LA, Rouleau JL, Pfeffer MA, Braunwald E. Effect of pravastatin on cardiovascular events in women after myocardial infarction: the cholesterol and recurrent events (CARE) trial. *J Am Coll Cardiol* 1998;32:140–6.
- [17] Serruys P, Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B. Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215–22.
- [18] Ogawa H, Kojima S. Clinical evidence for Japanese population based on prospective studies—linking clinical trials and clinical practice. *J Cardiol* 2009;54:171–82.
- [19] Delanty N, Vaughan CJ. Vascular effects of statins in stroke. *Stroke* 1997;28:2315–20.
- [20] Vaughan CJ, Gotto Jr AM, Basson CT. The evolving role of statins in the management of atherosclerosis. *J Am Coll Cardiol* 2000;35:1–10.
- [21] Werner N, Nickenig G, Laufs U. Pleiotropic effects of HMG-CoA reductase inhibitors. *Basic Res Cardiol* 2002;97:105–16.
- [22] Reilly SD, Litovsky SH, Steinkampf MP, Caulfield JB. Statins improve human coronary atherosclerotic plaque morphology. *Tex Heart Inst J* 2008;35:99–103.
- [23] Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;101:1899–906.
- [24] Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111–5.
- [25] Heitzer T, Schlinzig K, Krohn K, Meinertz T, Munzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* 2001;104:2673–8.
- [26] Higashi Y, Noma K, Yoshizumi M, Kihara Y. Endothelial function and oxidative stress in cardiovascular disease. *Circ J* 2009;73:411–8.
- [27] Munakata M, Ito N, Nunokawa T, Yoshinaga K. Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. *Am J Hypertens* 2003;16:653–7.
- [28] Lehmann ED, Hopkins KD, Rawesh A, Joseph RC, Kongola K, Coppack SW, Gosling RG. Relation between number of cardiovascular risk factors/events and non-invasive Doppler ultrasound assessment of aortic compliance. *Hypertension* 1998;32:565–9.
- [29] Van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, Hoeks AP, van der Kuip DA, Hofman A, Witteman JC. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke* 2001;32:454–60.
- [30] Ross R. Atherosclerosis is an inflammatory disease. *Am Heart J* 1999;138:S419–20.
- [31] Rifai N, Ridker OM. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. *Clin Chem* 2001;47:403–11.
- [32] Morcos E, Wiklund NP. Nitrite and nitrate measurements in human urine by capillary electrophoresis. *Methods Mol Biol* 2004;479:21–34.
- [33] Tsubakimoto A, Saito I, Mannami T, Naito Y, Nakamura S, Dohi Y, Yonemasu K. Impact of metabolic syndrome on brachial-ankle pulse wave velocity in Japan. *Hypertens Res* 2006;29:29–37.
- [34] Proudfoot J, Barden A, Mori TA, Burke V, Croft KD, Beilin LJ, Puddey IB. Measurement of urinary isoprostanes as markers of in vivo lipid peroxidation—a comparison of enzyme immunoassay with chromatography/mass spectrometry. *Anal Biochem* 1999;272:209–15.
- [35] Mezzetti A, Cipollone F, Cuccurullo F. Oxidative stress and cardiovascular complications in diabetes: isoprostane as a new marker on an old paradigm. *Cardiovasc Res* 2000;47:475–88.
- [36] Montuschi P, Barnes PJ, Roberts LJ. Isoprostanes: markers and mediators of oxidative stress. *FASEB J* 2004;18:1791–800.
- [37] Kato M, Dote K, Sasaki S, Ueda K, Kono Y, Naganuma T, Watanabe Y, Kajikawa M, Yokoyama H, Higashi A. Clinical impact of dyslipidemia for coronary plaque vulnerability in acute coronary syndrome without metabolic syndrome. *J Cardiol* 2009;54:394–401.
- [38] Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R. Long-term consequences of Kawasaki disease: a 10 to 21-year follow-up study of 594 patients. *Circulation* 1996;94:1379–85.
- [39] Suzuki A, Takemura A, Inaba R, Sonobe T, Tsuchiya K, Korenaga T. Magnetic resonance coronary angiography to evaluate coronary arterial lesions in patients with Kawasaki disease. *Cardiol Young* 2006;16:563–71.
- [40] Ishii M, Ueno T, Ikeda H, Iemura M, Sugimura T, Furui J, Sugahara Y, Muta H, Akagi T, Nomura Y, Homma T, Yokoi H, Nobuyoshi M, Matsuishi T, Kato H. Sequential follow-up results of catheter intervention for coronary artery lesions after Kawasaki disease: quantitative coronary arterial angiography and intravascular ultrasound imaging study. *Circulation* 2002;105:3004–10.
- [41] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *West*

- of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301–7.
- [42] Shah AS, Dolan LM, Kimball TR, Gao Z, Khoury PR, Daniels SR, Urbina EM. Influence of duration of diabetes, glycemic control, and traditional cardiovascular risk factors on early atherosclerotic vascular changes in adolescents and young adults with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2009;94:3740–5.
- [43] Schwab KO, Doerfer J, Krebs A, Krebs K, Schorb E, Hallermann K, Superti-Furga A, Zieger B, März W, Schmidt-Trucksäss A, Winkler K. Early atherosclerosis in childhood type 1 diabetes: role of raised systolic blood pressure in the absence of dyslipidaemia. *J Am Coll Cardiol* 1998;31:1330–5.
- [44] Mullen MJ, Clarkson P, Donald AE, Thomson H, Thorne SA, Powe AJ, Furuno T, Bull T, Deanfield JE. Effect of enalapril on endothelial function in young insulin-dependent diabetic patients: a randomized, double-blind study. *J Am Coll Cardiol* 1998;31:1330–5.
- [45] de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 2002;40:2122–4.
- [46] Ozawa S, Hamaoka K. HMG-CoA reductase inhibitors are effective for prevention of acute coronary artery injury in a rabbit model of Kawasaki disease. *J Am Coll Cardiol* 2006;46(Suppl. A):244A.
- [47] Ozawa S, Hamaoka K, Niboshi A, Iwasaki N. HMG-CoA reductase inhibitors (statins) is effective in the prevention of acute coronary injury in a rabbit model for Kawasaki disease. *Cardiol Young* 2006;16(Suppl.):62–3.
- [48] Bandoh T, Mitani H, Niihashi M, Kusumi Y, Kimura M, Ishikawa J, Totsuka T, Sakurai I, Hayashi S. Fluvastatin suppresses atherosclerotic progression, mediated through its inhibitory effect on endothelial dysfunction, lipid peroxidation, and macrophage deposition. *J Cardiovasc Pharmacol* 2000;35:136–44.
- [49] National Cholesterol Education Program (NCEP). Highlights of the report of the expert panel on blood cholesterol levels in children and adolescents. *Pediatrics* 1992;89:495–501.
- [50] Riegger G, Abletshauser C, Ludwig M, Schwandt P, Widimsky J, Weidinger G, Welzel D. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis* 1999;144:263–70.
- [51] Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Büller HR, Sijbrands EJ, Kastelein JJ. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;292:331–7.